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ANIMAL MODELS IN THE ASSESSMENT OF FIBER CARCINOGENESIS

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When lung cancer began to assume epidemic proportions - in the late 40's and early 50's - it became desirable to utilize animal models in order to explore etiologic factors and the pathogenesis of the disease. It seemed evident then, as it does now, that simply producing a tumor, any tumor, in a target organ was not truly a model. It simply contributed to answering the question of whether a material interacting with a biologic system can induce tumoral transformation. But tumors are disorders of tissues, not of organs, and transformation within tissues is governed by dose considerations, epigenetic influences, and reactivities specific to tissues.

There was the generally agreed on perception that the human tumors were bronchogenic and, indeed, that the common cigarette related cancer was a squamous cell or small cell undifferentiated tumor arising in bronchial epithelium. There were convincing demonstrations of the fact that the increase in lung cancer had occurred in these varieties - so-called Kreyberg I - and that the Kreyberg II (adenocarcinoma and large cell undifferentiated) had remained fairly stationary and were the types seen in non-smokers (Kreyberg,1962; Spain,1959).

The animal model of lung cancer with which we were most familiar was the so-called mouse adenoma or alveologenic carcinoma (Stewart et al,1979). This tumor,

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however, did not seem pertinent to human lung cancer because the tissue of origin was different even though the organ was the same. It was definitively genetically dominated which was not the situation in man, and the changes that led up to it were distinctly different from those that preceded the common lung cancer in humans as was the cell type.

Auerbach had demonstrated a series of precancerous alterations in the bronchi of smokers which preceded the common lung cancers. These were hyperplasia, squamous metaplasia, metaplasia with atypia, and carcinoma-in-situ (Auerbach et al,1961).

If one were to understand the ways in which inhaled toxicants contributed to the origin of lung cancer it was necessary, we thought, to develop a model which reproduced the staged series of events that led up to a "human" type of lung cancer.

Much effort and energy went into the development of such models and it was possible to reproduce the changes in the bronchial epithelium from metaplasia, to atypia, to cancer in situ, to invasive carcinoma which mirrored the events as they occurred in the human disease (Kuschner,1968). We learned that the etiology of the disease was probably multifactorial and that it involved the combined action of agents which stimulated proliferation, agents which produced squamous metaplasia, agents which were genotoxic - all of which were probably present in the melange of substances that made up tobacco smoke.

Were these experiences of any value in assessing human risk? Only in the broadest sense. The answers they gave were yes or no answers. They were not quantitative. Yes - the offending species of chromium was the hexavalent form. Yes - non-carcinogenic irritants could potentiate the effects of polycyclic aromatic hydrocarbons.

This was the background against which we initially tried to understand the action of carcinogenic fibers and develop models that would help us understand it. We failed. It has not, to my mind, been possible to produce a typical bronchogenic carcinoma in an experimental animal with fiber exposure.

This failure may be instructive. Cancer arising in the metaplastic lining of major bronchi may not be the tumor characteristic of fiber inhalation in man or in rodent species.

As time went on, our experience with human lung cancer began to change. It was noted that the profile of cell types was changing. Squamous cell cancer was becoming less frequent and adenocarcinoma and large cell undifferentiated were increasing (Vincent et al,1977). Auerbach repeated his study and found that cigarette smoke no longer produced precancerous bronchial epithelial changes with great frequency (Auerbach et al,1979). More recent studies have begun to identify changes at a different level of the air passages (now the peripheral air spaces) which I believe may precede malignant change (Miller,1990). These are focal areas of bronchoalveolar epithelial hyperplasia by some termed adenomas, most often multiple, which may progress to carcinoma.

This shift in location of precancerous change and in the origin and form now more characteristic of cigarette smokers has been attributed to the more peripheral site of action of more deeply inhaled, less irritating, low tar and low nicotine cigarettes.

Now I believe we can begin to understand the origins of the current lung cancer in smokers, begin to understand the particular contribution of fibers to carcinogenesis and understand, too, the requirements of the models we must use.

Fibers can, when they are of the proper character and dimension, lead to interstitial fibrosis. This is the capability of long, thin durable fibers (Wright and Kuschner,1977). It is reasonable to believe that the contribution of fibers to the development of lung cancer is by way of interstitial fibrosis. Experimental models have emphasized the inevitable and, I believe, necessary presence of fibrosis in experimentally induced lung cancer of fiber origin (Wagner et al,1974; Davis et al,1986; Davis and Jones,1988).

Attention has been drawn to the concommitant occurrence of asbestosis and lung cancer where the latter

develops in man (Kipen et al,1987; Hughes and Weill, 1991).

It is well worth remembering that other forms of interstitial fibrosis predispose to lung cancer (Watters,1988). These may be localized to the borders of focal scars (Spencer,1982) where the epithelium lining the air spaces in the peripheral interstices of the scar proliferates or there may be more generalized interstitial fibrosis as, for example, in idiopathic interstitial fibrosis, or scleroderma, where proliferating epithelium is the substrate on which cancer develops (Turner-Warwick,1980; Talbott et al,1980). Pathologists have been impressed by the continuity of change from the epithelial proliferative change that accompanies interstitial fibrosis to the cellular atypia and finally the cancer that may ensue from interstitial fibrosis (Heppleston,1988).

Certain caveats must be mentioned - animal models may be induced to produce interstitial fibrosis when that form of the reaction is not characteristic of the human response. Thus high dose finely divided silica in the experimental animal may produce interstitial fibrosis in a fashion not unlike the lesion of asbestosis. Tumors develop in association with such fibrotic lesions as a transition from the proliferative epithelial reaction that attends the fibrosis. The form of the fibrosis however, - the geography of the lesion - is quite unlike the human silicotic nodule. This latter typically perivascular lesion beginning and extending from peritruncal fibrosis is not accompanied by epithelial proliferation and cannot, therefore, be expected to contribute to carcinogenesis.

The model we seek, then, is an animal system which will produce spreading peribronchiolar interstitial fibrosis with associated epithelial proliferation. We have such a system in rats exposed to fibrogenic fibers. However, even this system is problematic. Human carcinoma associated with fibers appears to require the additional contribution of cigarette smoking (Mossman and Craighead,1987). This is not true of the rat lesions which progress from epithelial prominence and proliferation to cancer without an additional exogenous factor. In guinea pigs, on the other hand, marked asbestos

induced proliferation does not progress to cancer (Wright and Kuschner,1977). This suggests that our favored rat model operates with the assistance of some other factor, perhaps the presence of an oncogene. The rat may be an initiated species on which we superimpose the promoting effect of the epithelial proliferation associated with fiber induced fibrosis.

There is one further feature of lung carcinogenesis in the rat which is a cause for some uneasiness. Those of you familiar with the rat neoplasms will agree that we see two types of tumor. One is the scar associated tumor we have been discussing and the other is the expanding adenomatous to carcinomatous lesion with no apparent direct relationship to fibrotic scar although occurring in animals with fibrosis. Is it fair to count these two tumor types as if they were one as is often done? I'm not sure.

The other tumor we are anxious to model is mesothelioma. The demonstration first by Wagner (Wagner and Berry,1969) with the subsequent systematization by Stanton (Stanton and Wrench,1972) of the effect of materials introduced directly into the pleural cavity has presented us with a surfeit of riches. Virtually any fiber which, by virtue of its dimensions, evokes a fibrogenic response will produce a lenticular zone of scarring about which malignant transformation will occur. These fibrosarcomata are comparable to one form of the human tumor and occasionally the experimental tumors induced in this fashion resemble the epithelioid type of human tumor. They do, however, require the placement of a fair amount of foreign material within the mesothelial lined cavity. This maneuver bypasses characteristics which determine inhalation, deposition, translocation, and persistence. A material which when dumped directly into a mesothelial lined cavity may induce a mesothelioma may, in the normal course of inhalation exposure, never reach or never persist in the pleura in quantities sufficient to induce the tumor. It is noteworthy that the determinants of fibrogenicity, fiber dimension and fiber durability, are also determinants of mesothelioma producing capability. When mesothelioma is produced experimentally by inhalation, the foci of tumor formation can be seen to be associated with fibrosis resulting from the pleural effect of durable fiber.

These effects have been produced by inhalation with consistency and high incidence only with erionite and ceramic fiber. With the first, there has been a comparable human experience. Again we are seeing an all or none effect, since dose related risk assessment in animals has not been practical as yet without even approaching the problems of species extrapolation. It is fair to say that the contribution animal models have made to human risk assessment has been to begin to provide some answers to the question of could this material be carcinogenic? If yes, how did it bring this about? Are the same mechanisms operative under the conditions of human exposure?

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